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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/713,136	11/14/2000	Stephen Tuck	3778820001500	3530

25226 7590 12/16/2004

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EXAMINER	
HUYNH, PHUONG N	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 12/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/713,136	TUCK ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *9/21/04*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11-42,63,65-86,88,89,94-101 and 106-108* is/are pending in the application.

4a) Of the above claim(s) *11-42,65-70,73,76-82,85,88 and 89* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *63, 71-72, 74-75, 83-84, 86, 94-101 and 106-108* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *04 November 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/21/04 has been entered.

2. Claims 11-42, 63, 65-86, 88-89, 94-101, and 106-108 are pending.

3. Claims 11-42, 65-70, 73, 76-82, 85, and 88-89, are withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

4. Claims 63, 71-72, 74-75, 83-84, 86, 94-101 and 106-108, drawn to a population of conjugate molecules that read on the species "Amb a1" as the specific antigen and the "AACGTTCG" as a specific ISS, are being acted upon in this Office Action.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 63, 71-72, 74-75, 83-84, 86, 94-101 and 106-108 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) a population of conjugate molecules, said molecules comprising a ragweed pollen allergen Amb a1 and a polynucleotide wherein the polynucleotide consisting of an immunostimulatory sequence (ISS) selected from the group consisting of SEQ ID NO: 1-8 wherein the extent of conjugation in the population provides an average of at least 5.5 immunostimulatory sequence per antigen molecule, (2) The said population wherein the immunostimulatory sequence consisting of the sequence 5'-purine, purine, C, G, pyrimidine, pyrimidine, C, G-3', (3) the said population wherein the immunostimulatory sequence consisting of a sequence such as the ones set forth in claim 72, (4) a population of conjugate molecules, said molecules comprising a ragweed pollen allergen Amb a1 and a polynucleotide wherein the polynucleotide consisting of an immunostimulatory sequence

(ISS) selected from the group consisting of SEQ ID NO: 1-8 wherein the extent of conjugation in the population provides a ratio of (i) average mass of ISS to (ii) average mass of antigen of at least about 45 to about 40, (5) the population of conjugate molecules, said molecules comprising a ragweed pollen allergen Amb a1 and an immunostimulatory sequence (ISS) consisting of the sequence selected from the group consisting of SEQ ID NO: 1-8, wherein the extent of conjugation in the population in the population provides a ratio of (i) average mass of ISS to (ii) average mass of antigen of at least about 45 to about 40 wherein the ISS consisting of the sequence 5'-purine, purine, C, G, pyrimidine, pyrimidine, C, G-3' or a sequence such as the ones set forth in claim 84, (6) a composition comprising the population mentioned above in a pharmaceutically acceptable excipient, and (7) a population of conjugate molecules made by the process comprising: combining a polynucleotide consisting of an immunostimulatory sequence (ISS) of SEQ ID NO: 1 and an allergen at a ratio of about 17 molar equivalents of the polynucleotide to about 1 molar equivalent of the allergen whereby conjugate molecules comprising the polynucleotide and allergen are formed, wherein the polynucleotide is consisting of the sequence 5'-cytosine, guanine-3' for treating allergy, **does not** reasonably provide enablement for (1) *all* polynucleotide "comprising" any immunostimulatory sequence (ISS) comprises the sequence 5'cytosine, guanine-3' wherein polynucleotide is "greater than 6 and less than about 200 nucleotides in length" conjugated to the any antigen in the claimed population of conjugate molecules as set forth in claims 63, 75, and 108, (2) any ISS "comprises" the sequence 5'-purine, purine, C,G,pyrimidine, pyrimidine, C,G-3' (claims 71 and 83), (3) any ISS comprises any sequence (claims 72 and 84), (4) any "mammal allergen" as set forth in claims 96 and 100, (5) any antigen is any polypeptide as set forth in claims 106 and 107 in the claimed population of conjugate molecules or composition comprising said conjugates molecules as set forth in claims 63, 71-72, 74-75, 83-84, 86, and 94-101, and 106-108. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient

to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only eight specific immunostimulatory sequences (ISS) consisting of a nucleotide sequence selected from the group consisting of SEQ ID NO: 1-8. The specification discloses only one ragweed allergen Amb a1 conjugated to a polynucleotide consisting of SEQ ID NO: 1 (See page 71). The conjugate was prepared by incubation of a mixture of ISS at various molar concentrations such as 4, 7 or 17 molar to 1 molar concentration of Amb a1. The antibody response and histamine release from various conjugates such as AIC-L (4:1), AIC-M (7:1) and AIC-H (17-1) are measured. The AIC-H (17-1) conjugate shift the Th2 to Th1 immune response as determined by IFNγ, IL-5 levels and histamine release (page 80-82). The specification discloses the term "antigen" means any substance such as peptides, proteins, glycoproteins, polysaccharides, complex carbohydrates, sugars, gangliosides lipids, and phospholipids; portions thereof and combination thereof (page 16, lines 20-22). The specification discloses that the term "allergen" means antigen, or antigenic portion thereof of any molecule, usually a protein (see 18, lines 12-14).

The specification does not teach how to make any population of conjugate molecules mentioned above because the term "comprising" or "comprises" is open-ended. It expands the immunostimulatory sequence (ISS) to include additional undisclosed nucleotides at either or both ends so long the nucleotide sequence has a 5' cytosine and a 3' guanine. In addition to the problem of the undisclosed ISS, there is insufficient guidance as to the structure of the polynucleotide that is "greater than 6 and less than about 200 nucleotides in length" without the nucleotide sequence. Even if the ISS is limited to SEQ ID NO: 1, the specification discloses ISS consisting of SEQ ID NO: 1 is only 22 nucleotides in length. The rest of polynucleotide containing the ISS is not adequate taught in the specification without the nucleotide sequence. Further, there is insufficient guidance as to the structure of the "antigen" and "mammal allergen" without the amino acid sequence.

Stryer *et al* teach that a protein is highly dependent on the overall structure of the protein itself and that the primary amino acid sequence determines the conformational of the protein (See enclosed appropriate pages).

Ngo *et al* teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are

critical to maintain the protein's structure/function will require guidance (see Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495).

Chatel et al teach various factors such as antigen or allergen structure, mouse strain, CpG/recombinant protein expression influence the immune response (see entire document, abstract, in particular). Without the structure of the antigen and the polynucleotide, it is unpredictable which undisclosed antigen unconjugated to which undisclosed polynucleotide has stimulatory activity.

Van Uden *et al* (PTO 1449) teach even after intensive attempts to precisely define the DNA sequence structure required for immune stimulation, this most fundamental aspect of ISS is only partially understood (See page 903, in particular).

Segal *et al*, of record, teach that immunostimulatory sequences such as CpG oligonucleotides are potent adjuvant that triggering *autoimmune disease* in predisposed susceptible individual (See abstract, in particular).

Yamada *et al*, of record, teach that the sequence and length of a DNA strand determine its activity and depending on how these polynucleotide's secondary/tertiary structure are fold, activity may be gained or lost (See page 5593, column 2, second full paragraph, in particular). Given the unlimited number of antigen, and mammal allergen conjugated to unlimited number of polynucleotide comprising any ISS without the sequence, there is insufficient working examples demonstrating that the undisclosed population of conjugate molecules are immunostimulatory, let alone in vivo working example that population of conjugate molecules are useful for treating any disease. Without the structure of the antigen and the polynucleotide, one skill in the art cannot make, much less use the claimed invention. Since the antigen and polynucleotide in the conjugate molecules are not enabled, it follows that the composition comprising the undisclosed population of conjugate molecules in a pharmaceutically acceptable carrier is not enabled. It also follows that the mass of the ISS containing polynucleotide and the mass of the antigen cannot be determined without the nucleotide and amino acid sequences, respectively. Since the molecule weight of the antigen depends upon the amino acid sequence, without the amino acid sequence of the antigen, the molecular weight of the antigen cannot be determined. Likewise, the molecule weight of the polynucleotide comprising ISS depends on the nucleotide sequence, such double strand or single- stranded deoxyribonucleotide, single-stranded RNA, the length of such nucleotide. Without the information about the nucleotide sequence, one skill in the art cannot

determine the molecular weight, in turn the desired concentration of the molar ratio of the conjugate molecule.

For these reasons, it would require undue experimentation even for one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicants' arguments filed 9/21/04 have been fully considered but are not found persuasive.

Applicants' position is that the invention is based on the discovery that the ratio of ISS to antigen in a conjugate molecule can alter the immunostimulatory and biological activities of the conjugate molecule. For example, as the ratio of ISS to antigen increases for a population of conjugate molecules, the allergenicity of the molecules decreases, as does the ability of the molecules to stimulate antibody production. Thus, the claimed invention is directed to populations of ISS-antigen conjugate molecules with varying activities. Antigens for use in the claimed invention are well known in the art. Polynucleotides greater than 6 and less than about 200 nucleotides in length comprising an ISS, wherein the ISS comprising a CG dinucleotide, are also well known in the art. The invention lies in the unique combination and resultant activity of the ISS-antigen conjugate molecules prepared according to the instant specification. Oligonucleotides comprising ISS for use in the present invention are described in the specification and well known in the art. Contrary to the Examiner's assertion at page 6 of the Office Action that only eight specific immunostimulatory sequences are disclosed in the specification, pages 36-43 of the specification provide over 75 examples of ISS for use in the invention, as well as methods for making additional ISS-containing polynucleotides. At pages 66-69, the specification provides methods by which the skilled artisan can assess the activity of any ISS-containing polynucleotide. Applicants also submit that ISS comprising a CG dinucleotide were well known in the art at the time the application was filed and that the relative level of skill in the art is high. A review of the many references regarding CG-containing immunostimulatory

sequences cited in the specification and submitted to the Office clearly shows that a CG dinucleotide is a necessary element of the claimed category of immunostimulatory sequences. Such extensive disclosure provides adequate guidance such that a skilled artisan would be able to practice the invention without undue experimentation. The Examiner relies on the references of Van Uden, Segal and Yamada to support the lack of enablement rejection. Van Uden describes immunostimulatory DNA and it application to allergic disease. As noted by the Examiner, on page 903 Van Uden states that the precise CG DNA sequence structure required for immune stimulation ... is only partially understood." However, Van Uden then presents 36 CG-containing sequences as "potent immunostimulatory DNA sequences" in Table 1 and goes on to state that the dinucleotide 5'-CG-3' is generally required for immunostimulatory activity. See, for example, Van Uden page 904. All of the CG-containing sequences taught in Van Uden had immunostimulatory activity. Taken in its entirety, Van Uden teaches that a CG dinucleotide is a critical element for immunostimulatory activity of the oligonucleotide. Throughout, Segal refers to "CpG-containing oligonucleotides" as immunostimulatory and the only requirement taught for the immunostimulatory activity of an oligonucleotide by Segal is the presence of a CG dinucleotide. Thus, Segal teaches immunostimulatory activity of oligonucleotides containing a CG dinucleotide and presents nothing that conflicts with this. A skilled artisan reading Segal would not question the structural requirement for an immunostimulatory oligonucleotide. Segal does nothing to support the alleged lack of enablement of the claimed invention with regard to requirements for the claimed oligonucleotide structure. Applicants respectfully point out that Yamada describes feature of DNA sequences which suppress immune activation by immunostimulatory DNA, not features of the immunostimulatory DNA itself. In fact, Yamada is focused on the description of DNA sequences with suppressive activity and provides nothing to support the alleged lack of enablement of the instant invention. The Examiner further states that the term "comprising" expands the ISS to include additional undisclosed nucleotides at either or both ends so long the nucleotide sequence has a 5" i "2 Office Action, page 4. Applicants respectfully submit that the 5' cytosine and a 3' guanine inclusion of the term "comprising" with regard to the oligonucleotide in the claims leaves the claims fully enabled by the specification. As discussed, immunostimulatory oligonucleotides of varying lengths are well-known in the art. Van Uden, for example, describes immune stimulation associated with oligonucleotides and associated with gene vaccination from immunostimulatory sequences within a plasmid backbone. Thus, immunostimulatory sequences are known to be active with a variety of flanking sequences and a

variety of lengths. Applicants respectfully submit that none of these references, when taken in its entirety, support the alleged state of unpredictability with regard to the claimed invention and thus, do not provide acceptable documentation or sound scientific reasoning to support any doubt of the teachings of the specification.

In contrast to applicant's assertion that polynucleotides greater than 6 and less than about 200 nucleotides in length comprising an ISS, wherein the ISS comprising 5'cytocine and 3' guanine dinucleotide in the claimed population of conjugate molecules are well known in the art, Claim 63 as written merely requires population of conjugate molecule comprising any polynucleotide having a sequence greater than 6 and less than about 200 nucleotides comprising any ISS wherein the ISS having any nucleotide sequence so long the 5' end of the sequence is cytocine and the 3' end of the sequence is guanine. Claim 63 does not recite the unmethylated CpG dinucleotide as the immunostimulatory sequence known in the art.

The specification does not teach how to make any population of conjugate molecules mentioned above because the term "comprising" or "comprises" is open-ended. It expands the immunostimulatory sequence (ISS) to include additional undisclosed nucleotides at either or both ends so long the nucleotide sequence has a 5' cytosine and a 3' guanine. In addition to the problem of the undisclosed ISS, there is insufficient guidance as to the structure of the polynucleotide that is "greater than 6 and less than about 200 nucleotides in length" without the nucleotide sequence. Even if the ISS is limited to SEQ ID NO: 1, the specification discloses ISS consisting of SEQ ID NO: 1 is only 22 nucleotides in length. The rest of polynucleotides containing the ISS is not enabled in the specification without the nucleotide sequence. Further, there is insufficient guidance as to the structure of the "antigen" and "mammal allergen" without the amino acid sequence. Applicant's attention is referred to the detailed rejection stated above.

7. Claims 63, 71-72, 74-75, 83-84, 86, 94-101 and 106-108 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) *all* polynucleotide comprising any immunostimulatory sequence (ISS) comprises the sequence 5'cytosine, guanine-3' wherein polynucleotide is greater than 6 and less than about 200 nucleotides in length conjugated to the any antigen in the claimed population of conjugate

molecules as set forth in claims 63, 75, and 108, (2) any ISS "comprises" the sequence 5'-purine, purine, C,G, pyrimidine, pyrimidine, C,G-3' (claims 71 and 83), (3) any ISS comprises any sequence (claims 72 and 84), (4) any "antigen" as set forth in claims 63 and 75, (5) any "mammal allergen" as set forth in claims 96 and 100, (5) any antigen is any polypeptide as set forth in claims 106 and 107 in the claimed population of conjugate molecules or composition comprising said conjugates molecules as set forth in claims 63, 71-72, 74-75, 83-84, 86, 94-101 and 106-108.

The specification discloses only eight specific immunostimulatory sequences (ISS) consisting of a nucleotide sequence selected from the group consisting of SEQ ID NO: 1-8. The specification discloses only one ragweed allergen Amb a1 conjugated to a polynucleotide consisting of SEQ ID NO: 1 (See page 71). The conjugate was prepared by incubation of a mixture of ISS at various molar concentrations such as 4, 7 or 17 molar to 1 molar concentration of Amb a1. The antibody response and histamine release from various conjugates such as AIC-L (4:1), AIC-M (7:1) and AIC-H (17-1) are measured. The AIC-H (17-1) conjugate shift the Th2 to Th1 immune response as determined by IFNγ, IL-5 levels and histamine release (page 80-82). The specification discloses the term "antigen" means any substance such as peptides, proteins, glycoproteins, polysaccharides, complex carbohydrates, sugars, gangliosides lipids, and phospholipids; portions thereof and combination thereof (page 16, lines 20-22). The specification discloses that the term "allergen" means antigen, or antigenic portion thereof of any molecule, usually a protein (see 18, lines 12-14).

With the exception of the specific population of conjugates comprising the specific immunostimulatory sequence (ISS) and the specific allergen, there is inadequate written description about the structure associated with function of all polynucleotide comprising any immunostimulatory sequence (ISS) wherein the polynucleotide is greater than 6 and less than about 200 nucleotide in the claimed conjugate molecules without the nucleotide sequence. Further the term "comprising" is open-ended. It expands the polynucleotide to include additional nucleotides at either or both ends. Likewise, there is adequate written description for all ISS comprises the sequence 5'cytosine, guanine-3', all ISS such as the ones recited in claims 72 and 84 because the term "comprises" is open-ended. It expands the ISS in the conjugated molecules to include additional nucleotides at either or both ends. There is inadequate written about the nucleotides to be include at either or both ends. Even if the ISS is limited to SEQ ID NO: 1, the specification discloses ISS of SEQ ID NO: 1 is only 22 nucleotides in length. The rest of polynucleotide containing the ISS is not adequate described without the nucleotide sequence.

With regard to "antigen" is any polypeptide or any "mammal allergen" in the population of conjugated molecules, there is insufficient written description about the antigen or mammal allergen without the amino acid sequence. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.).

The specification as-filed does not provide adequate written description support for "antigen" and "mammal allergen" other than the specific allergen. Therefore, the skilled artisan can envision neither all the contemplated amino acid sequence of all antigen and all mammal allergen, polypeptide antigen, nor the function of any mammal allergen and polypeptide antigen. Consequently, conception in either case cannot be achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. The sequence itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, 1483. In Fiddes v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class.

Further, the specification discloses only *one* ragweed allergen Amb a1 conjugated to a polynucleotide consisting of SEQ ID NO: 1. Given the lack of a written description of *any* additional representative species of population of conjugate molecules wherein the molecule comprises any antigen, any allergen, any polypeptide and any polynucleotide comprising any ISS wherein the polynucleotide is less than about 200 nucleotides in length, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).* Since the antigen or mammal allergen and polynucleotide in the conjugate molecules are not adequately described, it follows that the composition comprising the undisclosed population of conjugate molecules in a pharmaceutically acceptable carrier is not adequately described.

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicants' arguments filed 9/21/04 have been fully considered but are not found persuasive.

Applicants' position is that (1) the claims are directed to conjugate molecules comprising a polynucleotide greater than 6 and less than about 200 nucleotides in length comprising an ISS, wherein the ISS comprises a CG dinucleotide. Disclosed in the specification, and known in the art are the structural characteristics of an oligonucleotide comprising an ISS required for a functional immunostimulatory oligonucleotide such that a skilled artisan would recognize possession of the claimed immunostimulatory oligonucleotides. See, for example, pages 36-37 of the specification. Applicants also note that Van Uden, cited by the Examiner, describes many CG-containing immunostimulatory oligonucleotides and, in turn, further cites a number of references describing additional CG-containing immunostimulatory oligonucleotides. The primary stated requirement for the immunostimulatory activity of the oligonucleotides in Van Uden is the presence of a CG dinucleotide. Thus, the connection between the 5'-CG-3' dinucleotide of the oligonucleotide and the immunostimulatory activity of the oligonucleotide was well known in the art at the time the instant application was filed. Quoting from the Office's Written Description Requirement Guidelines, the court in Enzo stated that the PTO has determined that the mitten description requirement can be met by (showing) that an invention is complete by disclose of sufficiently detailed, relevant identifying characteristics ... i.e., complete or partial structure, other physical and/or chemical properties.

In response, the specification discloses only eight specific immunostimulatory sequences (ISS) consisting of a nucleotide sequence selected from the group consisting of SEQ ID NO: 1-8. The specification discloses only one ragweed allergen Amb a1 conjugated to a polynucleotide consisting of SEQ ID NO: 1 (See page 71). The conjugate was prepared by incubation of a mixture of ISS at various molar concentrations such as 4, 7 or 17 molar to 1 molar concentration of Amb a1. The antibody response and histamine release from various conjugates such as AIC-L (4:1), AIC-M (7:1) and AIC-H (17-1) are measured. The AIC-H (17-1) conjugate shift the Th2 to Th1 immune response as determined by IFNγ, IL-5 levels and histamine release (page 80-82). The specification discloses the term "antigen" means any substance such as peptides, proteins, glycoproteins, polysaccharides, complex carbohydrates, sugars, gangliosides lipids, and

phospholipids; portions thereof and combination thereof (page 16, lines 20-22). The specification discloses that the term "allergen" means antigen, or antigenic portion thereof of any molecule, usually a protein (see 18, lines 12-14).

With the exception of the specific population of conjugates comprising the specific immunostimulatory sequence (ISS) and the specific allergen, there is inadequate written description about the structure associated with function of all polynucleotide comprising any immunostimulatory sequence (ISS) wherein the polynucleotide is greater than 6 and less than about 200 nucleotide in the claimed conjugate molecules without the nucleotide sequence. Further the term "comprising" is open-ended. It expands the polynucleotide to include additional nucleotides at either or both ends. Likewise, there is adequate written description for all ISS comprises the sequence 5'cytosine, guanine-3', all ISS such as the ones recited in claims 72 and 84 because the term "comprises" is open-ended. It expands the ISS in the conjugated molecules to include additional nucleotides at either or both ends. There is inadequate written about the nucleotides to be include at either or both ends. Even if the ISS is limited to SEQ ID NO: 1, the specification discloses ISS of SEQ ID NO: 1 is only 22 nucleotides in length. The rest of polynucleotide containing the ISS is not adequate described without the nucleotide sequence.

With regard to "antigen" is any polypeptide or any "mammal allergen" in the population of conjugated molecules, there is insufficient written description about the antigen or mammal allergen without the amino acid sequence. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.).

The specification as-filed does not provide adequate written description support for "antigen" and "mammal allergen" other than the specific allergen. Therefore, the skilled artisan can envision neither all the contemplated amino acid sequence of all antigen and all mammal allergen, polypeptide antigen, nor the function of any mammal allergen and polypeptide antigen. Consequently, conception in either case cannot be achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. The sequence itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai

Pharmaceutical Co. Ltd., 18 USPQ2d 1016. One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, 1483. In Fiddes v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class.

Further, the specification discloses only *one* ragweed allergen Amb a1 conjugated to a polynucleotide consisting of SEQ ID NO: 1. Given the lack of a written description of *any* additional representative species of population of conjugate molecules wherein the molecule comprises any antigen, any allergen, any polypeptide and any polynucleotide comprising any ISS wherein the polynucleotide is less than about 200 nucleotides in length, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).* Since the antigen or mammal allergen and polynucleotide in the conjugate molecules are not adequately described, it follows that the composition comprising the undisclosed population of conjugate molecules in a pharmaceutically acceptable carrier is not adequately described. Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

8. Claims 63, 71-72, 74-75, 83-84, 86, 94-101 and 106-108 are rejected under 35 U.S.C. 112, first paragraph, containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection.**

The "greater than **6** and less than about 200 nucleotides" in Claims 63, 75 and 108 represents a departure from the specification and the claims as originally filed. The specification discloses only "greater than **8** and less than about 200 nucleotides" on page 43, line 1-3.

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

10. Claims 71, 83, 96 and 100 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The "5'purine" in claim 71 has no antecedent basis in base claim 63 because "purine" consists of A or G. However, the amended claim 63 requires that the ISS comprises 5' cytosine (C), which is a pyrimidine.

The "5'purine" in claim 83 has no antecedent basis in base claim 75 because "5'-purine" consists of A or G. However, the amended claim 75 requires that the ISS begins with 5' cytosine (C), which is a pyrimidine.

The "mammal allergen" in claims 96 and 100 is ambiguous and indefinite because it is not clear which mammal the allergen belongs.

Applicants' arguments filed 9/21/04 have been fully considered but are not found persuasive.

Applicants' position is that (1) Claims 63 and 75 recite that the ISS includes a CG dinucleotide. The claims use the conventional notation of "5'-cytosine, guanine-3' " to indicate the order of the cytosine and guanine relative to each other in the polynucleotide sequence.

The Examiner bases this rejection on the impression that "the amended claim 63 requires that the ISS comprises 5' cytosine (C)." Office Action, page 10. As apparent from the enablement rejection of the outstanding Office Action, the Examiner has understood the phrase "said ISS comprises s'-cytosine, guanine-3'" to indicate that the ISS includes "additional undisclosed nucleotides at either or both ends so long the nucleotide sequence has a 5' cytosine and a 3' guanine." Office Action, page 4. This interpretation of this phrase is unfortunately incorrect and the ISS do not require a terminal 5' cytosine and a terminal 3' guanine. As described in the specification and well known in the art, a CG (i.e., cytosine, guanine) dinucleotide is a necessary element of the claimed category of immunostimulatory sequences. The specification describes this, for example, on pages 36-37, in addition to listing over 75 examples of ISS for use in the invention. As can be seen, all of these ISS examples include at least one CG dinucleotide. Contrary to the Examiner's interpretation of the claim language, none of the examples have a C on the 5' end and a G on the 3' end. As outlined herein, the ISS of the claimed invention comprises a CG dinucleotide. The references of Van Uden, Segal and Yamada cited by the Examiner also support Applicants' view of the claim language, i.e. an ISS comprising a CG

dinucleotide as opposed to the Examiner's apparent view of a nucleotide with a terminal 5' cytosine and a terminal 3' guanine.

In response, Applicant is reminded that enablement rejection under 35 U.S.C. 112 first paragraph, is a separate rejection from the rejection under 35 U.S.C. 112, second paragraph.

The "5'purine" in claim 71 has **no antecedent basis** in claim 63 because claim 63 recites "....ISS comprises 5'-cytosine, guanine-3'...". Claim 63 does not recite the "5'-cytosine, guanine-3" is the CG dinucleotide within the ISS as argued. Claim 63 as written refers to ISS having a sequence begins with 5' cytocine (c) and ends with Guanine (G) at the 3' end instead of 5' purine, purine (i.e. A or G), C, G, pyrimidine, pyrimidine, C, G-3' in dependent claim 83. To provide antecedent basis in claim 71, claim 63 must be amended. Likewise, the same reasons apply to claim 83.

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claims 63, 71 and 94 are rejected under 35 U.S.C. 102(b) as being anticipated by Klinman et al (Vaccine 17: 19-25, Jan 1999; PTO 892).

Klinman *et al* teach a composition comprising a population of conjugate molecules wherein said conjugate molecule comprise an antigen such as Ovalbumin (Ova) and polynucleotide comprising an immunostimulatory sequence (ISS) such as 5'C, G-3' (see underline CG, page 20, col. 1, Reagent, in particular) wherein the reference polynucleotide is (GCTAGACGTTAGCGT) which is greater than 6 and less than about 200 nucleotide in length and wherein the extent of conjugation is 20 μg of Ova to 12-200 μg of CpG containing GCTAGACGTTAGCGT (see page 24, col. 1, Table 1, and caption, in particular). The reference 20 μg of Ova to 200 μg of CpG containing GCTAGACGTTAGCGT is 10 ISS-containing polynucleotides per antigen molecule (see 200 divided by 20) and the number of ISS to antigen on average is inherently at least 5.5 because streptavidin binding to biotin is tetravalent and streptavidin reacts in two fold excess to biotinylated Ova or biotinylated ISS (see page 20, col. 2, first paragraph, in particular). The reference ISS GCTA**GA**CG**TT**AG**CG**T comprises unmethylated CpG dinucleotides flanked by two 5' purine such as G and A, and two '3

pyrimidines such as T and T. The term "comprising" is open-ended. It expands the claimed ISS to include additional nucleotide at either or both ends. Klinman et al teach the reference conjugates such as CpG oligo-avidin-OVA extremely immunogenic and at optimal CpG oligo mass: OVA ratios, IgG antibody production increased tenfold over Ova-avidin or OVA alone (see page 22, col. 2, second paragraph, Figure 3, in particular). Claim 94 is included in this rejection because the reference ovalbumin inherently is also an allergen. Thus, the reference teachings anticipate the claimed invention.

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

15. Claims 75, and 83 are rejected under 35 U.S.C. 103(a) as being unpatentable over in view of Klinman et al (Vaccine 17: 19-25, Jan 1999; PTO 892).

The teachings of Klinman *et al* have been discussed supra. Klinman et al teach the reference conjugates such as CpG oligo-avidin-OVA extremely immunogenic and at optimal CpG oligo mass: OVA ratios, IgG antibody production increased tenfold over Ova-avidin or OVA alone (see page 22, col. 2, second paragraph, Figure 3, in particular).

The invention in claim 75 differs from the teachings of the reference only in that population wherein the extent of conjugation in the population provides a ratio of (i) average mass of ISS-containing polynucleotide to (ii) average mass of antigen of at least about 45 to about 40 (about 1.1).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to optimize the ratio of average mass of ISS-containing polynucleotide to average mass of antigen for a population of conjugate molecules comprising any antigen and polynucleotide comprising ISS as taught by Klinman et al. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Klinman et al teach the reference conjugates such as CpG oligo-avidin-OVA extremely immunogenic and at optimal CpG oligo mass: OVA ratios, IgG antibody production increased tenfold over Ova-avidin or OVA alone (see page 22, col. 2, second paragraph, Figure 3, in particular). Further, it is within the purview of one ordinary skilled in the conjugate chemistry to optimize the weight ratio or the mass of CpG oligo to the mass of the antigen based on the type of linker used. Further, it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. In re Aller, 220 F2d 454,456,105 USPQ233; 235 (CCPA 1955). See MPEP § 2144.05 part IIA.

16. Claims 63, 71-72, 75, 83-84, 86, 94-101, 106 and 107 are rejected under 35 U.S.C. 103(a) as being unpatentable over in view of Klinman et al (Vaccine 17: 19-25, Jan 1999; PTO 892) in view of WO 98/16247 (of record, April 1998; PTO 892).

The teachings of Klinman *et al* have been discussed supra.

The invention in claims 72 and 84 differs from the teachings of the reference only in that the population of conjugate molecules wherein the ISS comprises a sequence of AACGTTCG.

The invention in claim 86 differs from the teachings of the reference only in that a composition comprising the population of conjugates and a pharmaceutically acceptable carrier.

The invention in claim 98 differs from the teachings of the reference only in that the population of conjugate molecules wherein the antigen is an allergen.

The invention in claims 95 and 99 differs from the teachings of the reference only in that the population of conjugate molecules wherein the allergen is Amb a1.

The invention in claims 96 and 100 differs from the teachings of the reference only in that the population of conjugate molecules wherein the allergen is a pollen allergen, an insect allergen, a mammal allergen.

The invention in claims 97 and 101 differs from the teachings of the reference only in that the population of conjugate molecules wherein the allergen is a ragweed allergen, a grass allergen, a birch allergen, a dust mite allergen, or a cat allergen.

The invention in claims 106 and 107 differs from the teachings of the reference only in that the population of conjugate molecules wherein the antigen is a polypeptide.

The WO 9/16247 publication teaches a composition comprising a population of conjugate molecules comprising antigen such as IMM antigen (see page 7, line 13, in particular) or and a polynucleotide comprising an immunostimulatory sequence (ISS) such as ISS-PN (See page 12, lines 20-27, page 14, lines 21-25, in particular). The reference ISS sequence such as CpG motif is flanked by two purine (e.g., GA or AA) and at least two pyrimidine nucleotides (see page 15, lines 1-6, in particular). The reference polynucleotide is at least 6 bases in length and preferably are between 6 and 200 bases in length to enhance the uptake of the reference conjugate into the targeted tissues (see page 15, lines 7-9, in particular). The WO 9/16247 publication further teaches the reference ISS comprises 5'-TGACTGTG**AACGTTCG**AGATGA-3' (see page 36, line 10, in particular). The term "comprises" is open-ended. It expands the claimed ISS to include the reference ISS. The WO 9/16247 publication teaches the reference antigen is a recombinant protein or polypeptide (see page 18, line 5, in particular), allergen such as dust mite allergens Der pI, Der pII, ragweed pollen allergen such as Amb a I, insect allergen such as phospholipase A2 from bee, birch pollen, cat allergen such as Fel dI, tree pollen, and grass pollen (see paragraph bridging page 19 and 20, in particular). The WO 9/16247 publication teaches a pharmaceutical composition comprising the reference conjugate molecules and a pharmaceutically acceptable carrier such as saline and buffered media (see page 30, lines 3-15, in particular). The WO 9/16247 publication teaches the advantages of the reference conjugate molecules are that these molecules boost the host's immune response toward a Th1 phenotype to avoids the risk of immunization induced anaphylaxis, suppress IgE production in response to a sensitizing allergen (see page 11, lines 24-27, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to the antigen in the conjugate molecules as taught by the Klinman et al for the allergen such as Amb a I or insect allergen such as phospholipase A2 from bee, birch pollen, cat allergen such as Fel dI, tree pollen, or grass pollen as taught by the WO 9/16247 publication. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the WO 9/16247 publication teaches the advantages of the reference conjugate molecules are that these molecules boost the host's immune response toward a Th1 phenotype to avoids the risk of immunization induced anaphylaxis, suppress IgE production in response to a sensitizing allergen (see page 11, lines 24-27, in particular). Klinman et al teach the reference conjugates such as CpG oligo-avidin-OVA extremely immunogenic and at optimal CpG oligo mass: OVA ratios, IgG antibody production increased tenfold over Ova-avidin or OVA alone (see page 22, col. 2, second paragraph, Figure 3, in particular).

17. Claim 108 is free of prior art.

18. No claim is allowed.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (571) 273-8300.

20. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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